General

Guideline Title

Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline.

Bibliographic Source(s)

Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, Samuels MH. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016 Nov;101(11):3888-921. [281 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group
YES	Methodologist Involvement

	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
	Search Strategy
	Study Selection
	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
	Grading the Quality or Strength of Evidence
	Benefits and Harms of Recommendations
	Evidence Summary Supporting Recommendations
	Rating the Strength of Recommendations
	Specific and Unambiguous Articulation of Recommendations
	External Review
	Updating

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

October 25, 2016 – Testosterone and Other Anabolic Androgenic Steroids (AAS) : The U.S. Food and Drug Administration (FDA) approved class-wide labeling changes for all prescription testosterone products, adding a new Warning and updating the Abuse and Dependence section to include new safety information from published literature and case reports regarding the risks associated with abuse and dependence of testosterone and other AAS.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (+OOO, ++OO, +++O, and ++++); the strength of the recommendation (1 or 2); and the difference between a "recommendation" and a "suggestion" are provided at the end of the "Major Recommendations" field.

Diagnosis of Hypopituitarism

Central Adrenal Insufficiency

The Task Force suggests measuring serum cortisol levels at 8-9 AM as the first-line test for diagnosing central adrenal insufficiency (AI). (2|+OOO)

The Task Force recommends against using a random cortisol level to diagnose AI. (1|++OO)

The Task Force suggests that a cortisol level <3 µg/dL is indicative of AI and a cortisol level >15 µg/dL likely excludes an AI diagnosis. (2|+OOO)

The Task Force suggests performing a corticotropin stimulation test when morning cortisol values are between 3 and 15 µg/dL to diagnose AI. Peak cortisol levels <18.1 µg/dL (500 nmol/L) at 30 or 60 minutes indicate AI. (2|++OO)

The Task Force suggests that clinicians perform biochemical testing for the hypothalamic-pituitary-adrenal (HPA) axis at least 18-24 hours after the last hydrocortisone (HC) dose or longer for synthetic glucocorticoids (GCs). (2|++OO)

Central Hypothyroidism

The Task Force recommends measuring serum free thyroxine (T4) (fT4) and thyroid-stimulating hormone (TSH) to evaluate central hypothyroidism (CH). An fT4 level below the laboratory reference range in conjunction with a low, normal, or mildly elevated TSH in the setting of pituitary disease usually confirms a CH diagnosis. (1|++++)

In patients with pituitary disease and low-normal fT4 levels suspected to have mild CH, the Task Force suggests starting levothyroxine (L-T4) if suggestive symptoms are present or following fT4 levels over time and starting treatment if the fT4 level decreases by 20% or more. (2|+OOO)

The Task Force suggests against using dynamic TSH-secretion testing to diagnose CH. (2|+++O)

Growth Hormone (GH) Deficiency

In patients with suspected GH deficiency (GHD), the Task Force recommends GH stimulation testing. Single GH measurements are not helpful. (1|+++O)

The Task Force recommends using appropriately controlled body mass index (BMI) cutoffs to assess peak GH values. (1|++OO)

The Task Force suggests against biochemical testing for GHD in patients with clear-cut features of GHD and three other documented pituitary hormone deficits. (2|+++O)

Central Hypogonadism in Males

In males with suspected hypogonadism, the Task Force recommends measuring serum testosterone (T), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) to diagnose central hypogonadism. (1|++OO)

The Task Force recommends that clinicians perform hormonal testing for central hypogonadism in males in the absence of acute/subacute illness and before 10 AM (after overnight fast) combined with serum prolactin (PRL). (1|++OO)

Central Hypogonadism in Females

In the presence of oligomenorrhea or amenorrhea, the Task Force recommends measuring serum estradiol (E2), FSH, and LH. Clinicians should exclude other causes of menstrual irregularities related to impaired ovulation (hyperprolactinemia, hyperandrogenism, and thyroid disease), particularly if no other pituitary hormone deficits are present. In cases of amenorrhea, clinicians should also exclude pregnancy. (1|++OO)

The Task Force suggests against dynamic testing with gonadotrophin-releasing hormone (GnRH), which

offers no useful diagnostic information. (2|++OO)

The Task Force recommends that in postmenopausal women, the absence of high serum FSH and LH is sufficient for a diagnosis of gonadotrope dysfunction (provided the patient is not on hormonal replacement therapy [HRT]). (1|+++O)

Central Diabetes Insipidus

The Task Force recommends simultaneously measuring serum and urine osmolarity in patients with polyuria (more than 50 mL/kg of body weight/24 hours, 3.5 L/day in a 70-kg person). In the presence of high serum osmolarity (>295 mOsmol/L), urine osmolarity should reach approximately 600 mOsmol/L (urine osmolality/plasma osmolality ratio should be ≤2), whereas urine dipstick should be negative for glucose. (1|+++O)

Treatment

Hormonal Replacement in Panhypopituitarism

Glucocorticoid Replacement

The Task Force recommends using HC, usually 15–20 mg total daily dose in single or divided doses. Patients using divided doses should take the highest dose in the morning at awakening and the second in the afternoon (two-dose regime) or the second and third at lunch and late afternoon, respectively (three-dose regime). (1|+++O)

The Task Force suggests using longer-acting GCs in selected cases (e.g., nonavailability, poor compliance, convenience). (2|+OOO)

The Task Force recommends that clinicians teach all patients with AI regarding stress-dose and emergency GC administration and instruct them to obtain an emergency card/bracelet/necklace regarding AI and an emergency kit containing injectable high-dose GC (1|+++O)

The Task Force recommends against using fludrocortisone in patients with secondary AI. (1|+++O)

Adrenal Crisis

The Task Force recommends that clinicians treat patients with suspected adrenal crisis (AC) due to secondary AI with an immediate parenteral injection of 50–100 mg HC. (1|+++O)

Thyroid Hormone Replacement

The Task Force recommends levothyroxine (L-T4) in doses sufficient to achieve serum fT4 levels in the mid to upper half of the reference range. Appropriate L-T4 doses in CH average 1.6 µg/kg/day, with dose adjustments based on clinical context, age, and fT4 levels. (1|+++O)

The Task Force suggests against treating CH with levotriiodothyronine (L-T3), thyroid extracts, or other formulations of thyroid hormones. (2|++OO)

The Task Force recommends against using serum TSH levels to adjust thyroid replacement dosing in patients with CH. (1|+++O)

Testosterone Replacement

The Task Force suggests T replacement for adult males with central hypogonadism and no contraindications in order to prevent anemia related to T deficiency; reduce fat mass; and improve bone mineral density (BMD), libido, sexual function, energy levels, sense of well-being, and muscle mass and strength. (2|++OO)

Estrogen Replacement in Premenopausal Women

The Task Force recommends gonadal hormone treatment in premenopausal women with central hypogonadism, provided there are no contraindications. (1|+++O)

GH Replacement Therapy

The Task Force recommends offering GH replacement to those patients with proven GHD and no contraindications. The Task Force recommends a starting dose of 0.2–0.4 mg/d for patients younger than 60 years and 0.1–0.2 mg/d for patients older than 60 years. (1|+++O)

The Task Force recommends titrating GH doses and maintaining insulin-like growth factor-1 (IGF-1) levels below the upper limit of normal and reducing the dose if side effects manifest. (1|+OOO)

The Task Force suggests against administering GH to elderly adults with age-adjusted low IGF-1 levels and no history of pituitary or hypothalamic disease. (2|+OOO)

The Task Force recommends against using GH to enhance athletic performance because this practice is illegal in the United States, has poor scientific or ethical justification, and does not have substantiated efficacy. (Ungraded Good Practice Statement)

Diabetes Insipidus

When administering desmopressin (DDAVP) in diabetes insipidus (DI), the Task Force suggests individualized therapeutic schedules. Although clinicians should offer therapy to all patients, some patients with partial DI may not be bothered by polyuria and may prefer no treatment. To reduce the risk of hyponatremia, the Task Force recommends that clinicians educate all patients receiving DDAVP about the risk of overdosing. Periodically (at least weekly), patients should experience a phase of polyuria during which the effect of the medication has obviously worn off. (Ungraded Good Practice Statement)

In postpituitary surgery DI, the Task Force suggests that clinicians should make at least one attempt to discontinue DDAVP during the weeks/months after surgery to determine whether posterior pituitary function has recovered. (Ungraded Good Practice Statement)

In cases of adipsic DI, the Task Force suggests careful DDAVP and fluid intake titration that includes frequent weighing and serum sodium level monitoring. (Ungraded Good Practice Statement)

The Task Force suggests that all patients with DI wear an emergency bracelet or necklace to inform clinicians of the patient's health problem if incapacitated. (Ungraded Good Practice Statement)

Interactions between Replacement Hormones

Glucocorticoids and GH

The Task Force suggests testing HPA axis functionality before and after starting GH replacement in patients who are not receiving GC replacement and who have demonstrated apparently normal pituitary-adrenal function. (2|+OOO)

Glucocorticoids and Thyroid Hormone

The Task Force suggests evaluating patients with CH for AI before starting L-T4 therapy. If this is not feasible, clinicians should prescribe empiric GC therapy in patients with CH who are starting L-T4 therapy until there is a definitive evaluation for AI. (2|++OO)

Glucocorticoids and Estrogen

The Task Force suggests that when clinicians assess adrenal reserve or the adequacy of HC replacement, they take into consideration that total serum cortisol level can be elevated due to the effects of estrogen on corticosteroid-binding globulin (CBG). (2|+++O)

GH and Thyroid Hormones

The Task Force recommends that clinicians monitor euthyroid patients with GHD who begin GH therapy for the risk of developing CH, and if fT4 levels decrease below the reference range, these patients should begin L-T4 therapy. CH patients with GHD who are already receiving L-T4 may require increased L-T4 doses when they begin GH therapy to maintain fT4 levels within target ranges. (1|++OO)

The Task Force suggests clinicians treat CH before performing GH stimulation testing because CH may impair the accurate diagnosis of GHD. (2|++OO)

Estrogen and Thyroid Hormones

In patients with CH requiring changes in estrogen therapy, the Task Force recommends monitoring fT4 levels and adjusting L-T4 doses to maintain fT4 levels within target ranges. (1|+++O)

GH and Estrogen

The Task Force suggests that women on oral estrogen replacement receive higher GH doses compared with eugonadal females or males. (2|+++O)

Glucocorticoids and Diabetes Insipidus

Because AI may mask the presence of partial DI, the Task Force suggests monitoring for the development of DI after starting GC replacement. Conversely, patients with improved DI without an AI diagnosis should undergo AI testing. (2|+OOO)

Risk of Hormonal Over-Replacement in Hypopituitarism

Bone Disease

Clinicians should individually assess GC replacement and avoid over-replacement to reduce the risk of osteoporosis. The Task Force suggests low-dose HC replacement because this approach might be associated with increased bone formation and a positive bone-remodeling balance. (2|++OO)

In men with hypopituitarism over-replaced with GC and at risk for fractures, the Task Force suggests vertebral fracture assessment (baseline plain spinal x-rays or dual-energy x-ray absorptiometry) to identify patients with unsuspected vertebral fractures. (2|++OO)

The Task Force suggests clinicians monitor L-T4 replacement, as recommended in previous sections, and avoid over-replacement to reduce the risk of fractures. (2|++OO)

Cardiovascular Risks in Patients with Hypopituitarism on Replacement Therapy

Glucocorticoid Over-Replacement

In patients with central AI, the Task Force recommends using the lowest tolerable dose of HC replacement to potentially decrease the risks of metabolic and cardiovascular disease. (1|+++O)

Thyroid Replacement

To avoid the possible long-term cardiovascular risks of insufficient or excess thyroid hormone treatment, clinicians should adjust L-T4 doses to avoid low or elevated fT4 levels in CH. (Ungraded Good Practice Statement)

Special Circumstances

Cushing's Disease

The Task Force recommends GC replacement until full HPA axis recovery after surgically resecting adrenocorticotropic hormone (ACTH)-secreting tumors. (1|+++O)

After curative surgery for Cushing's disease, the Task Force recommends retesting thyroid and GH axes before starting replacement treatment. (1|+OOO)

Prolactinomas

The Task Force recommends reassessing all pituitary axes in patients with macroprolactinoma and central hypogonadism who have had successful dopamine agonist treatments. (1|+++O)

GH Replacement in Cured Acromegaly after Surgery and/or Radiation

The Task Force suggests low-dose GH replacement in patients with cured acromegaly and documented GHD in the absence of known contraindications. (2|+OOO)

Perioperative Management of Hypopituitarism

Pituitary Surgery

The Task Force recommends using stress doses of steroids in AI before surgery and tapered doses after surgery before repeating testing. (1|+++O)

In patients with normal preoperative adrenal function, the Task Force suggests an individualized clinical approach for postoperative GC administration until the HPA axis can be evaluated. (2|++OO)

With preoperative CH, the Task Force recommends using L-T4 therapy before nonemergency surgery and throughout the perioperative period. (1|+++O)

With intact preoperative thyroid function, the Task Force recommends measuring fT4 levels 6 to 8 weeks postoperatively to assess for CH. (1|++OO)

The Task Force suggests that initial therapy for DI utilizes short-acting subcutaneous (sc) aqueous antidiuretic hormone (ADH), allowing for safer use in the vast majority of cases in whom DI resolves spontaneously. (2|++OO)

The Task Force does not suggest prescheduled DDAVP dosages in the first week postsurgery because of the risk of hyponatremia after transient DI resolves and the risk of syndrome of inappropriate ADH secretion that may occur 7 to 10 days after surgery. (2|+OOO)

The Task Force suggests oral or intranasal DDAVP after discharge, with clear instructions that patients should only use the medication if significant polyuria occurs. (2|+OOO)

The Task Force suggests retesting all pituitary axes starting at 6 weeks after pituitary surgery and then periodically to monitor the development or resolution of pituitary deficiencies. (2|++OO)

Non-Pituitary Surgery

On the day of surgery, the Task Force recommends adjusting GC doses according to the severity of illness and magnitude of the stressor. (1|+++O)

In cases of minor to moderate surgical stress, the Task Force suggests 25–75 mg HC per 24 hours (usually for 1–2 days). (2|++OO)

In cases of major surgical stress, the Task Force suggests a 100-mg HC per intravenous (iv) injection followed by a continuous iv infusion of 200 mg HC per 24 hours (alternatively 50 mg every 6 hours iv or intramuscular [im]). (2|++OO)

Management of Hypopituitarism in Pregnancy

Glucocorticoids

The Task Force suggests using HC as the preferred GC in pregnancy and increasing the dose based on the individual clinical course; higher doses may be required, in particular during the third trimester. (Ungraded Good Practice Statement)

The Task Force suggests that pregnant patients with central AI be closely monitored for clinical symptoms and signs of GC over- and under-replacement (e.g., normal weight gain, fatigue, postural hypotension or hypertension, hyperglycemia). (Ungraded Good Practice Statement)

The Task Force recommends against using dexamethasone in pregnancy because it is not inactivated in the placenta. (1|++OO)

The Task Force recommends HC stress dosing during the active phase of labor, similar to that used in major surgical stress. (1|++OO)

Thyroid

The Task Force recommends that clinicians monitor fT4 or total T4 levels every 4 to 6 weeks for women with CH who become pregnant, and that these women may require increased L-T4 doses to maintain levels within target ranges for pregnancy. (1|++OO)

Desmopressin

In pregnant women with pre-existing DI, the Task Force suggests continuing DDAVP during pregnancy and adjusting doses if required. (2|++OO)

Growth Hormone

The Task Force suggests discontinuing GH replacement during pregnancy because there is no clear evidence yet for efficacy or safety, and the placenta produces GH. (2|++OO)

Management of Hypopituitarism in Pituitary Apoplexy

The Task Force recommends testing for acute pituitary insufficiency in all patients with pituitary apoplexy. (1|+++O)

Because acute AI is a major cause of mortality, the Task Force recommends GC therapy until a laboratory diagnosis is established and the patient maintains normal pituitary function. (1|++OO)

The Task Force recommends that clinicians monitor pituitary axes in pituitary apoplexy patients treated with either surgical decompression or conservative management because hypopituitarism may develop over time. (1|++OO)

Treatment of Hypopituitarism in Patients Receiving Antiepileptic Medications

The Task Force suggests clinicians educate AI patients that are taking nondexamethasone GCs and who start enzyme-inducing antiepileptic drugs (AEDs) about the early signs and symptoms of AI. (2|++OO)

In patients with AI on dexamethasone, the Task Force suggests increasing dexamethasone replacement doses if enzyme-induced AEDs are coadministered. (2|+OOO)

In CH patients receiving L-T4, the Task Force recommends checking fT4 at least 6 weeks after starting an AED and increasing L-T4 doses if fT4 levels decrease below the target range. (1|++OO)

In women who have started estrogen replacement, the Task Force suggests evaluating AED levels and adjusting AED doses as required. (2|++OO)

The Task Force suggests monitoring DDAVP doses and making further adjustments as needed in patients who are started on AEDs. (2|++OO)

Definitions

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Ungraded Good Practice Statement: In this guideline, the Task Force made several statements to

emphasize the importance of shared decision making, general preventive care measures, and basic principles of hormonal replacement in hypopituitarism. The Task Force labeled these as "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not systematically appraised; therefore, the Task Force considers these statements out of the scope of this guideline. The intention of these statements is to draw attention to and remind providers of these principles; one should not consider these statements as graded recommendations.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Hypopituitarism, including the following conditions:

- Adrenal insufficiency
- Hypothyroidism
- Growth hormone deficiency
- Hypogonadism
- Diabetes insipidus
- Hypopituitarism during pregnancy

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Obstetrics and Gynecology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To formulate clinical practice guidelines for hormonal replacement in hypopituitarism in adults

Target Population

Adult patients with hypopituitarism

Interventions and Practices Considered

Diagnosis/Evaluation

- Measuring serum cortisol levels for diagnosing central adrenal insufficiency (AI)
- Performing a corticotropin stimulation test to diagnose AI
- Biochemical testing for the hypothalamic-pituitary-adrenal (HPA) axis
- Measuring serum free thyroxine (T4) (fT4) and thyroid-stimulating hormone (TSH) to evaluate central hypothyroidism (CH)
- Dynamic TSH-secretion testing to diagnose CH (recommendation against)
- Growth hormone (GH) stimulation testing to diagnose GH deficiency
- Using appropriately controlled body mass index (BMI) cutoffs to assess peak GH values
- Measuring serum testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin to diagnose central hypogonadism in males
- Serum estradiol (E2), FSH, and LH to diagnose central hypogonadism in females
- Dynamic testing with gonadotrophin-releasing hormone (GnRH) to diagnose central hypogonadism in females (recommendation against)
- Measuring serum and urine osmolarity in patients with polyuria to diagnose diabetes insipidus (DI)

Treatment/Management

- Hormonal replacement in panhypopituitarism
  - Hydrocortisone
  - Longer-acting glucocorticoids (GC)
  - Stress-dose and emergency GC administration/obtaining an emergency card/bracelet/necklace
  - Fludrocortisone in patients with secondary AI (recommendation against)
  - Treatment of adrenal crisis
  - Thyroid hormone replacement (levothyroxine)
  - Testosterone replacement
  - Estrogen replacement in premenopausal women
  - GH replacement
  - Desmopressin (DDAVP) in DI
- Monitoring patients for interactions between replacement hormones
  - Testing HPA axis functionality before and after starting GH replacement
  - Evaluating patients with CH for AI before starting levothyroxine therapy
  - Evaluating effects of estrogen on corticosteroid-binding globulin (CBG) when assessing serum cortisol
  - Monitoring interactions between GH and thyroid hormones
  - Ensuring that women on oral estrogen replacement receive higher GH doses compared with eugonadal females or males
  - Monitoring for the development of DI after starting GC replacement
- Monitoring for hormonal over-replacement to reduce risk of osteoporosis and fractures
- Using the lowest tolerable dose of HC and levothyroxine replacement to decrease the risks of metabolic and cardiovascular disease
- Considerations for hypopituitarism in special circumstances:
  - Cushing's disease and replacement treatment following surgery

Prolactinomas
GH replacement in cured acromegaly after surgery and/or radiation
Perioperative management of hypopituitarism (pituitary and nonpituitary surgery)
Management of hypopituitarism in pregnancy
Management of hypopituitarism in pituitary apoplexy
Treatment of hypopituitarism in patients receiving antiepileptic medications

Major Outcomes Considered

- Appropriateness of biochemical testing
- Adverse effects of hormone replacement therapy
- Pituitary tumor recurrence and secondary malignancy
- Stroke and other cardiovascular risks
- All-cause mortality
- Quality of life (QOL)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guideline Task Force commissioned two systematic reviews (see the "Availability of Companion Documents" field) to assist with summarizing the evidence base for this guideline.

Mortality in Patients with Panhypopituitarism

The reviewers searched several electronic databases including Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from earliest inception to December 8, 2014. The search was expanded to include any language. The search strategy was designed and conducted by an experienced librarian with input from the principal investigator. Controlled vocabulary supplemented with keywords was used to search for panhypopituitarism mortality.

Two reviewers independently screened titles and abstracts based on the inclusion criteria. The reviewers used the web-based platform DistillerSR (Evidence Partners Inc) to manage screening and data extraction. Relevant studies were retrieved for full text screening. The reviewers determined the methodological quality of studies and collected descriptive, methodological and outcome data. Any disagreements were resolved by a third reviewer. Full-text screening was also conducted in duplicates, any inclusion or exclusion disagreements were discussed and resolve by a third investigator.

Growth Hormone Replacement in Patients with Panhypopituitarism

The reviewers searched several electronic databases including Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from earliest inception to December 8, 2014. The search was expanded to include any language. The search strategy was designed and conducted by an experienced librarian with input from the principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies of the risk of pituitary tumor recurrence, secondary malignancy, or stroke associated with growth hormone replacement.

Two reviewers independently screened titles and abstracts based on the inclusion criteria. The reviewers used the web-based platform DistillerSR (Evidence Partners Inc) to manage screening and data extraction. Relevant studies were retrieved for full text screening. The reviewers determined the methodological quality of studies and collected descriptive, methodological and outcome data. Any disagreements were resolved by a third reviewer. Full-text screening was also conducted in duplicates, any inclusion or exclusion disagreements were discussed and resolved by a third investigator. Agreement between reviewers was evaluated using chance-adjusted agreement statistic.

Inclusion criteria were the following: adults requiring growth hormone (GH) replacement after pituitary disease/resection (could include patients who were treated as children but outcome ascertainment is in adulthood). Any studies that did not meet the inclusion criteria were excluded.

Number of Source Documents

Mortality in Patients with Panhypopituitarism

Five relevant observational studies were identified.

Growth Hormone Replacement in Patients with Panhypopituitarism

Seven studies that reported on pituitary tumor recurrence and 2 studies that reported on secondary malignancies were identified. Reviewers did not find studies that reported the outcome of stroke.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The guideline Task Force commissioned two systematic reviews (see the "Availability of Companion Documents" field) to assist with summarizing the evidence base for this guideline.

Mortality in Patients with Panhypopituitarism

The reviewers determined the methodological quality of studies and collected descriptive, methodological and outcome data. Any disagreements were resolved by a third reviewer.

The reviewers calculated rate of events from each study. They then pooled the log transformed event rates using the DerSimonian and Laird random-effect models with the heterogeneity estimated from the Mantel-Haenszel model. To measure the overall heterogeneity across the included studies, the reviewers used I^2 statistic, where I^2 >50% suggests high heterogeneity. All statistical analyses were conducted using OpenMeta Analyst.

Growth Hormone Replacement in Patients with Panhypopituitarism

The reviewers determined the methodological quality of studies and collected descriptive, methodological and outcome data. Any disagreements were resolved by a third reviewer. Agreement between reviewers was evaluated using chance-adjusted agreement statistic.

The reviewers calculated rate of events from growth hormone (GH) replacement arm and non-GH replacement arm. They then pooled the log transformed event rates using the DerSimonian and Laird random-effect models with the heterogeneity estimated from the Mantel-Haenszel model. To measure the overall heterogeneity across the included studies, reviewers used I^2 statistic, where I^2>50% suggests high heterogeneity. All statistical analyses were conducted using OpenMeta Analyst.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Participants

The participants include an Endocrine Society-appointed Task Force of six experts, a methodologist, and a medical writer. The American Association for Clinical Chemistry, the Pituitary Society, and the European Society of Endocrinology co-sponsored this guideline.

Evidence

The Task Force developed this evidence-based guideline using the Grading of Recommendations Assessment, Development and Evaluation system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process

One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, the American Association for Clinical Chemistry, the Pituitary Society, and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Ungraded Good Practice Statement: In this guideline, the Task Force made several statements to emphasize the importance of shared decision making, general preventive care measures, and basic principles of hormonal replacement in hypopituitarism. The Task Force labeled these as "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not systematically

appraised; therefore, the Task Force considers these statements out of the scope of this guideline. The intention of these statements is to draw attention to and remind providers of these principles; one should not consider these statements as graded recommendations.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Committees and members of the Endocrine Society, the American Association for Clinical Chemistry, the Pituitary Society, and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate evaluation and management of hypopituitarism in adults, including appropriate biochemical assessments, specific therapeutic decisions to decrease the risk of co-morbidities due to hormonal over-replacement or under-replacement, and managing hypopituitarism during pregnancy, pituitary surgery, and other types of surgeries

Refer to the evidence and remarks sections in the original guideline document for discussions of potential benefits of specific recommendations.

Potential Harms

- Side effects of growth hormone (GH) replacement at the recommended doses manifest in about 20% of patients and are usually reversible by lowering the GH dose. Reported side effects include fluid retention, arthralgias, myalgias, paresthesias, carpal tunnel syndrome, sleep apnea, sleep disturbances, and dyspnea. If replacement doses are too high, insulin resistance with diabetes may occur. Although the development of new cancers and new-onset diabetes is of concern, the safety profile for GH treatment (using appropriate replacement doses) appears favorable in long-term surveillance studies.
- Over-replacement with glucocorticoid (GC) in male patients with pituitary dysfunction can increase

vertebral fracture risk, despite the restoration of gonadal status. Levothyroxine (L-T4) over-replacement in patients with primary hypothyroidism may increase bone turnover and increase the fracture risk, especially in postmenopausal women. Similarly, in a cautionary study in 74 adult central hypothyroidism (CH) patients treated with 1.1 µg/kg/d L-T4, higher daily L-T4 doses were associated with a higher prevalence of vertebral fractures (assessed by lateral spine x-rays).

- In a cross-sectional study, hydrocortisone (HC) doses above 30 mg/day were associated with adverse health status by validated self-assessment questionnaires.
- Higher GC replacement doses in patients with adrenocorticotropic hormone (ACTH) deficiency were associated with increased overall and cardiovascular mortality; the greatest risk was in patients receiving daily HC doses higher or equal to 30 mg.
- Some antiepileptic drugs (AEDs) enhance hepatic cytochrome P450 (CYP450) isoenzyme activity (e.g., phenytoin, carbamazepine, oxcarbazepine, and topiramate), accelerating the hepatic metabolism of hormonal preparations and decreasing serum concentrations of relevant hormones. Effects depend on the type of GC.
- A recent publication reported that increased risk of vertebral fracture in hypopituitary patients receiving higher daily doses of L-T4 correlated with higher free thyroxine (fT4) levels.

Refer to the evidence and remarks sections in the original guideline document for additional discussions of potential risks and harms of specific recommendation.

Qualifying Statements

Qualifying Statements

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Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, Samuels MH. Hormonal replacement in hypopituitarism in adults: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2016 Nov;101(11):3888-921. [281 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

The Endocrine Society - Professional Association

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Guideline Committee

Hormonal Replacement in Hypopituitarism in Adults Task Force

Composition of Group That Authored the Guideline

Task Force Members: Maria Fleseriu (*Chair*); Ibrahim A. Hashim; Niki Karavitaki; Shlomo Melmed; M. Hassan Murad; Roberto Salvatori; Mary H. Samuels

Financial Disclosures/Conflicts of Interest

The Endocrine Society maintains a rigorous conflict of interest review process for developing clinical practice guidelines. All Task Force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The Clinical Guidelines Subcommittee (CGS) reviews all conflicts of interest before the Society's Council approves the members to participate on the Task Force and periodically

during the development of the guideline. All those participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and a majority of these participants must be without any conflicts of interest. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

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Financial Disclosures of the Task Force*

Maria Fleseriu, MD, FACE (Chair)—Financial or business/organizational interests: The Pituitary Society (board of directors), Novo Nordisk (principal investigator, research support to university, no direct compensation), Pfizer (principal investigator, research support to university, no direct compensation), Pfizer (scientific consultant); Significant financial interest or leadership position: None declared. Ibrahim A. Hashim, PhD—Financial or business/organizational interests: None declared; Significant financial interest or leadership position: None declared. Niki Karavitaki, PhD, FRCP—Financial or business/organizational interests: Society for Endocrinology, United Kingdom (member of the clinical committee), Pfizer (educational consultant); Significant financial interest or leadership position: None declared. Shlomo Melmed, MB, ChB, MACP, FRCP—Financial or business/organizational interests: The Pituitary Society (editor-in-chief, board of directors); Significant financial interest or leadership position: Pfizer (principal investigator, research grant). M. Hassan Murad, MD, MPH**—Financial or business/organizational interests: Mayo Clinic Evidence-based Practice Center; Significant financial interest or leadership position: None declared. Roberto Salvatori, MD—Financial or business/organizational interests: The Pituitary Society (member), Novo Nordisk (advisory board); Pfizer (scientific consultant); Significant financial interest or leadership position: None declared. Mary H. Samuels, MD—Financial or business/organizational interests: None declared; Significant financial interest or leadership position: None declared.

*Financial, business, and organizational disclosures of the Task Force cover the year before publication. Disclosures before this time period are archived.

**Evidence-based reviews for this guideline were prepared under contract with the Endocrine Society.

Guideline Endorser(s)

American Association for Clinical Chemistry, Inc. - Professional Association

European Society of Endocrinology - Medical Specialty Society

The Pituitary Society - Professional Association

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available to subscribers from the Journal of Clinical Endocrinology and Metabolism Web site .

Availability of Companion Documents

The following are available:

Jasim S, Alahdab F, Ahmed AT, Tamhane SU, Donegan D, Sharma A, Murad MH. Growth hormone replacement in patients with panhypopituitarism. Rochester (MN): Evidence based practice center, Knowledge and Evaluation Research Unit, Mayo Clinic; 2015 Apr 13. 21 p.
Jasim S, Alahdab F, Ahmed AT, Tamhane SU, Murad MH. Mortality in patients with panhypopituitarism. Rochester (MN): Evidence based practice center, Knowledge and Evaluation Research Unit, Mayo Clinic; 2015 Apr 13. 16 p.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on June 26, 2017. The information was verified by the guideline developer on July 31, 2017.

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